REMARKS

Introductory Comments

Claims 17-28 were examined in the Office Action under reply and were variously rejected under (1) 35 U.S.C. §112, first paragraph as containing new matter (claims 24 and 28); (2) 35 U.S.C. §112, second paragraph, as indefinite (claims 17-28); and (3) 35 U.S.C. §103(a) (claims 17-25). These rejections are traversed and believed to be overcome for reasons discussed below.

Applicants note that claims 26-28 were not subject to any art rejections. Moreover, applicants acknowledge with appreciation the withdrawal of all of the previous rejections.

Overview of the Amendments

The specification has been amended to indicate trademarks by capital letters, as requested by the Examiner. Claims 17, 19, 20, 22, 24, 26 and 28 have been amended to make minor wording changes suggested by the Examiner. Amendment of the claims is without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Entry of the amendments is respectfully requested.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 24 and 28 were rejected under 35 U.S.C. §112, first paragraph as containing new matter. In particular, the Office asserts the recitation "polylactic acids and/or polyglycolic acids" is not supported in the application. Although applicants disagree, claims 24 and 28 have been amended to eliminate the term "and/or" and inserted the term "or" in its place. As acknowledged by the Office, there is indeed support for a composition comprising polylactic acid or polyglycolic acids. Thus, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 17-28 were rejected under 35 U.S.C. §112, second paragraph, as indefinite. In particular, claims 17, 20, 22 and 26 were considered confusing based on minor wording informalities. Applicants have amended these claims as suggested by the Examiner. Additionally, claim 19 was rejected based on improper antecedence. Applicants have amended claim 19 to recite "protein carrier" thereby mirroring the language of claim 18 from which claim 19 depends. Accordingly, the foregoing bases for rejection have been overcome and withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. §103(a)

Claims 17-23 and 25 were rejected under 35 U.S.C. §103(a) as unpatentable over Costantino et al., *Vaccine* (1992) 10:691-698 ("Costantino") and van der Voort et al., *Infect. Immun.* (1996) 64:2745-2751 ("van der Voort") in view of Paradiso et al., *Dev. Biol. Stand.* (1996) 87:269-275 ("Paradiso"). The Office asserts Costantino teaches an NmC-CRM_{197} conjugate vaccine with aluminum hydroxide and a method of inducing an immune response to NmC. The Office acknowledges Costantino does not teach the use of NmB vesicles but cites van der Voort as teaching a hexavalent NmB outer membrane vesicle vaccine. Paradiso is said to teach immunogenic glycoconjugates of NmC saccharides covalently linked to CRM_{197}. The Office also asserts Paradiso teaches using OMVs from virulent NmB strains and "in the future, it will be desirable to mix them with a vaccine comprising group C meningococcal conjugate to create a new set of formulation." Office Action, page 5. However, applicants do not agree that the cited combination renders the present claims obvious.

Section 2142 of the MPEP sets forth the following basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify the references or combine reference teachings; (2) there must be a reasonable expectation of success (for the modification); and (3) the prior art references must teach or suggest all of the claim limitations. Furthermore, the teaching or suggestion and the reasonable

expectation of success must both be found in the prior art, not in applicants' disclosure. The Office has failed to satisfy these criteria. Applicants submit there is no motivation to modify the references as suggested by the Examiner and there is no reasonable expectation of success regarding the use of combination vaccines as claimed by applicants based on the cited art.

In particular, all of the present claims pertain to immunogenic compositions comprising (1) an NmC oligosaccharide conjugated to a carrier and (2) NmB proteoliposomic vesicles. None of the cited art, either alone or in combination, teaches or suggests the claimed combination. Specifically, as previously explained to the Office, Costantino is believed to **teach away** from the claimed invention. Costantino pertains to a meningococcus A and C conjugate vaccine. The authors do not describe or suggest using the A and C conjugate vaccine with an NmB protein, let alone an NmB proteoliposomic vesicle preparation. In fact, Costantino teaches that in order for an NmB vaccine to be efficacious, the polysaccharide must be conjugated to CRM_{197}. Costantino, at page 691 states:

> In the case of group B *N. meningitidis*, a vaccine is not yet available because the purified capsular polysaccharide is not immunogenic in humans. Poor immunogenicity in children is a limitation shared by many polysaccharides as a consequence of their T-independent character. This drawback has usually been overcome by coupling immunogenic proteins to polysaccharides or oligosaccharides to convert these antigens to a T-dependent form...This approach seems able to overcome also the poor immunogenicity of meningococcus B polysaccharide.

Thus, Costantino does not suggest combining a conjugated NmC oligosaccharide with an NmB component, especially an NmB component provided as proteoliposomic vesicles.

The van der Voort reference does not make up for the deficiencies in Costantino. Van der Voort pertains to a hexavalent vaccine made from six engineered strains of NmB. However, the reference fails to discuss or suggest the use of the NmB vaccine with other meningococcal serogroups, such as NmC. Thus, neither of Costantino

or van der Voort either alone or together provide a motivation to combine the conjugated NmC oligosaccharide with NmB proteoliposomic vesicles.

Finally, Paradiso does not provide the motivation to combine Costantino and van der Voort, as suggested by the Office. The Office alleges that Paradiso provides this motivation by expressly teaching "that it is desirable to mix a group C meningococcal conjugate with outer membrane vesicles prepared from group B meningococcal strains containing an array of proteins and lipids to create a new set of formulation." Office Action, page 5. However, the passage found at pages 272-273, bridging paragraph of Paradiso, cited by the Office, is taken completely out of context. In fact, the sentence reads "Since these vesicle preparations contain an array of proteins and lipids, the combinations will create a new set of formulation **challenges not unlike those encountered in mixing conjugate vaccines with DTP**." (Emphasis added.) The Office has left off the salient part of the sentence (in bold) when quoting this passage. In fact, Paradiso actually bolsters the patentability of the present claims by acknowledging that the preparation of combination vaccines is not a straight-forward task, without potential problems. As previously explained to the Examiner and supported by the statement from Paradiso quoted above, it is well known that certain mixtures of immunogens can actually be less effective than the individual components due to physical interactions of the individual immunogens which might result in altered conformation, aggregation or precipitation. Immunological dominance or competition between component immunogens is also known to occur. Finally, the FDA requires that the efficacy of new mixtures be shown even if the efficacy of the individual components or other mixtures using the individual components has been demonstrated, further evidencing the unpredictable results obtained with new mixtures.

The cited combination therefore does not disclose or suggest the claimed invention. Rather, a careful reading of the references teaches away from the claimed subject matter. To reiterate, Costantino teaches away from the use of NmB proteoliposomic vesicles and Paradiso explicitly supports the position that combination vaccines using NmB outer membrane vesicles mixed with other meningococcal

serogroups could present challenges. Thus, it is evident that the cited combination gives neither a suggestion nor an expectation of success for the use of such a combination vaccine, and both must be present in the prior art in order for the Patent Office to provide a *prima facie* case of obviousness. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

Based on the foregoing, the rejection of claims 17-23 and 25 over the stated combination should be withdrawn.

Claim 24 was rejected under 35 U.S.C. §103(a) over the combination of Costantino, van der Voort and Paradiso, as applied above, and further in view of U.S. Patent No. 6,413,520 to Granoff ("Granoff"). The Examiner acknowledges the combination of Costantino, van der Voort and Paradiso does not teach a composition with polylactic acids or polyglycolic acids. Granoff is cited for teaching such carriers. However, the cited combination is not believed to render claim 24 obvious.

As explained above, the combination of Costantino, van der Voort and Paradiso does not teach or suggest a compositions including NmB proteoliposomes and conjugated NmC oligosaccharides. Granoff, when applied to this combination, does not supply the missing elements. Granoff relates to methods for boosting an immune response against meningococcus by first administering a meningococcal A and C oligosaccharide-protein conjugate and subsequently boosting with a tetravalent meningococcal A, C, Y, W135 polysaccharide vaccine. The reference does not pertain to, or even mention, NmB proteolipsomic vesicles. Thus, there would be no motivation to include polylactic or polyglycolic acids in a combination vaccine containing the same. Thus, this combination is also inapplicable to the claimed invention and withdrawal of the rejection of claim 24 under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims define an invention that is complies with the requirements of 35 U.S.C. §112 and that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please send all further written communications in this case to:

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Respectfully submitted,

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